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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/987,456	11/14/2001	Maurice Zauderer	1821.0070004/EKS/EJH/TAC	6770

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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 04/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/987,456	ZAUDERER ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *84-122 and 127-131* is/are pending in the application.

4a) Of the above claim(s) *85-87,98,100-102 and 104-106* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *84,88-97,99,103,107-122 and 127-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/7/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed December 7, 2004 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

3. Claims 84-131 were pending. Applicants amended claims 84, 109 and 112. In addition, Applicants canceled claims 123-126. Therefore, claims 84-122 and 127-131 are currently pending.

4. Claims 85-87, 98, 100-102, 104-106 are drawn to non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim.

5. Therefore, claims 84, 88-97, 99, 103, 107-122 and 127-131 are examined on the merits in this action.

Withdrawn Objections/Rejections

6. The New Matter, Written Description and Enablement rejections under 35 U.S.C. 112, first paragraph are withdrawn in view of Applicants' arguments and/or amendments. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 103

7. Claims 84, 88-97, 99, 103, 107-122 and 127-131 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rowlands et al. (WO 93/01296) (Date of Patent is **January 21, 1993**) and Zauderer et al. (WO 00/28016) (Date of Patent is **May 18, 2000**) and Waterhouse et al. (Waterhouse, P.; Griffiths, A.D.; Johnson, K.S.; Winger, G. "Combinatorial infection and in vivo recombination: a strategy for making large phage antibody repertoires" *Nucleic Acids Research*, **1993**, 21, 9, 2265-2266).

For ***claims 84, 88, 96-97, 113, 117***, Rowlands et al. (see entire document) teach a method for producing antibodies in vaccinia infected cells that reads on the presently claimed invention (e.g., see Rowlands et al., abstract). For example, Rowlands et al. teach **[a-c]** the use of a population of mammalian host cells (e.g., see page 4, paragraph 2; see also paragraph bridging pages 7-8) for introducing and expressing a first/second polynucleotide encoding, through operable association with a transcriptional control region a first/second immunoglobulin polypeptide comprising both heavy/light chain constant/variable regions and a signal peptide for secretion using a vaccinia virus vector (e.g., see claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter"; see also page 2, middle paragraph, "An antibody molecule is composed of two light chains and two heavy chains ... Each heavy chain has at one end a variable domain followed by a number of constant domains, and each light chain has a variable domain at one end and a constant

domain at the other end"; see especially page 4, second full paragraph, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form"). Rowlands et al. do not explicitly state that a "signal" peptide is being used, but the Examiner contends that this feature is inherent in the method disclosed by Rowlands et al. because the fully functional recombinant antibody would not be "secreted" unless it has such a sequence. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

In addition, Rowlands et al. disclose **[d]** contacting said immunoglobulin molecules or fragments thereof with an antigen and detecting specific antigen-antibody complexes (e.g., see pages 18-19 and Table I wherein the Campath 1H antigen was "contacted" with said immunoglobulin molecules and "detection" was carried out using both T-cell and antigen binding assays). Finally, Rowlands et al. disclose **[e]** recovering the vaccinia virus vectors containing polynucleotides of said first library which encode immunoglobulin subunits polypeptides which, as part of an immunoglobulin molecule, or

antigen-specific fragment thereof are specific for said antigen (e.g., see page 5, paragraph 1, step 4, wherein the virus is "harvested" several times [i.e., recovered and/or isolated]).

For ***claim 103***, Rowlands et al. disclose a T7 phage promoter active in cells in which T7 RNA polymerase is expressed (e.g., see page 8, paragraph 2, "Expression levels of the two chains of the antibody can be enhanced by use of T7 polymerase to amplify the gene under the control of the T7 promoter").

For ***claims 121-122***, Rowlands et al. disclose ELISA (e.g., see page 18, line 7).

The prior art teachings of Rowlands et al. differ from the claimed invention as follows:

For ***claim 84***, Rowlands et al. are deficient in that they do not specifically teach the use of a "library" of first/second polynucleotides.

For ***claims 89-91***, Rowlands et al. do not disclose repetitive steps for "biopanning" a library.

For ***claims 92-95***, Rowlands et al. do not provide "isolating" steps.

For ***claim 99***, Rowlands et al. do not disclose an MOI of 1.

For ***claim 107, 110, 127-131***, Rowlands et al. do not disclose method steps for "tri-molecular" recombination.

For ***claims 108-109, 111-112***, Rowlands et al. do not disclose v7.5/tk or vEL/tk virus genomes with NotI/ApaI restriction sites.

For ***claims 114-116, 118-120***, Rowlands et al. do not disclose the use of virus "pools."

However, Zauderer et al. and Waterhouse et al. teach the following limitations that are deficient in Rowlands et al.:

For ***claim 84***, Zauderer et al. (see entire documents) teach the use of a "library" of polynucleotides in a vaccinia virus vector using the "tri-molecular recombination" approach for screening purposes (e.g., see Zauderer et al., page 52, lines 13-16, "The high yield of viral recombinants in tri-molecular recombination makes it possible, for the first time, to efficiently construct genomic or cDNA libraries in a vaccinia virus derived vector"; see also page 15, paragraph 1; see also page 22, last two paragraphs; see also Example 6 on pages 42-52). In addition, Waterhouse et al. teach that a "library" can be usefully employed to screen for antibodies with high affinity to various antigens including the use of heavy/light chains that are "packaged together" (see Waterhouse et al., page 2265, column 1; see also paragraph bridging pages 2265-2266). The Examiner further notes that Applicants' elected mammalian "HeLa" cells are disclosed also by Zauderer et al. (e.g., see Zauderer et al., page 32, line 2).

For ***claims 89-91***, Zauderer et al. disclose the use of vaccinia virus library vectors that require the use of a helper virus (i.e., are "incapable of producing infectious vaccinia virus") to infect host cells (e.g., see Zauderer et al., paragraph bridging pages 97-98, "Vaccinia virus DNA is not infectious as the virus cannot utilize cellular transcriptional machinery ... Previously ... non-homologous poxvirus fowlpox ... have been utilized as helper virus for packaging"). Zauderer et al. also indicate that the steps for introducing said vectors into host cells, permitting the expression of said vectors, contacting said expressed antibodies with an antigen and recovering said vectors can be repeated as

needed to increase the specificity and/or binding affinity (e.g., see page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure").

For ***claims 92-95***, Zauderer et al. disclose "isolating" the polynucleotides contained in the vaccinia virus vectors (e.g., see Zauderer et al., page 52, lines 20-23; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves combining isolated fractions]").

For ***claim 99***, Zauderer et al. disclose, for example an MOI = 1 (e.g., see page 86, line 2).

For ***claims 107, 110, 127-131***, Zauderer et al. disclose "tri-molecular" recombination, which includes, for example, cleavage of v7.5/tk or vEL/tk virus genomes with NotI/ApaI restriction enzymes and "one" transfer plasmid containing TKL/TKR and a library of human immunoglobulin genes containing both heavy and light genes to form vaccinia virus vectors via homologous recombination and method steps for screening and purifying said vectors repeated as many times as are needed to produce the desired products (e.g., see pages 48-52, sections 5.2-5.3; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves combining isolated fractions]"; see also claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide]

containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter").

For ***claims 108, 111***, Zauderer et al. disclose both v7.5/tk and vEL/tk (e.g., see figure 1).

For ***claims 109, 112***, Zauderer et al. disclose both NotI and ApaI (e.g., see figure 10).

For ***claims 114-116, 118-120***, Zauderer et al. disclose the use of "virus pools" (e.g., see page 51, last paragraph, especially line 27; see also page 58, Table V wherein multiple cycles are disclosed; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves combining isolated fractions]").

It would have been obvious to one skilled in the art at the time the invention was made to make a library of vaccinia virus vectors as taught by Zauderer et al. to express fully functional antibodies as taught by Rowlands et al. for the purpose of screening and/or affinity maturation as taught by Waterhouse et al. because Zauderer et al. explicitly state that their libraries can be efficiently produced using the tri-molecular recombination approach with the vaccinia virus vectors (like the vaccinia virus vectors disclosed by Rowlands et al.) and Waterhouse et al. teach that such a library would be useful in screening and affinity maturation. Thus, one of ordinary skill in the art would have been motivated to make the libraries as taught by Zauderer et al. using the heavy/light chain antibodies as disclosed by Rowlands et al. because Zauderer et al.

explicitly state that the their "tri-molecular" approach represents an easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells, which is a preferred embodiment for Rowlands et al. (e.g., see Zauderer et al., page 22, lines 14-17, "Major advantages of these infectious [vaccinia] viral vectors are ... the ease and efficiency with which recombinants can be introduced mammalian cells"). In addition, Waterhouse et al. teach that "associated" light and heavy chains are a "preferred" embodiment for screening and/or affinity maturation because they can be "simultaneously co-selected" (e.g., see Waterhouse et al., page 2265, paragraph 2; see also page 2265, column 1; see also paragraph bridging pages 2265-2266 wherein the usefulness of combinatorial antibody libraries is disclosed), which would encompass the "associated" heavy/light chains described by Rowlands et al. Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Zauderer et al. teach several successful examples of library formation using the same vaccinia virus vectors that are disclosed by Rowlands et al. and Waterhouse et al. teach several successful examples of associated light/heavy chains that can be used for screening and/or antibody maturation, which would encompass the heavy/light chain antibodies disclosed by Rowlands et al.

Response

8. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified

from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "... the Examiner has pointed to nothing specific in Rowlands, Zauderer, or Waterhouse that would have motivated or suggested one of ordinary skill in the art the desirability of combining these references (e.g., see 12/7/04 Response, page 31, second paragraph).

[2] Applicants argue, "While Rowlands describes the expression of a single, recombinant antibody using a vaccinia virus vector, there is no suggestion provided therein that would have motivated one of ordinary skill in the art to construct first and second libraries of polynucleotides in vaccinia virus vectors. Furthermore ... there is no suggestion to one of ordinary skill in the art to introduce into a population of mammalian host cells first and second vaccinia virus expression libraries encoding immunoglobulins as in the present invention" (e.g., see 12/7/04 Response, page 31, second paragraph).

[3] Applicants argue, "Waterhouse does not even describe vaccinia virus vectors or mammalian host cells ... Hence, there is absolutely nothing in Waterhouse to suggest ... to construct vaccinia virus expression libraries encoding human immunoglobulin subunit polypeptides for use in selecting polynucleotides which encode an antigen-specific human immunoglobulin ... Waterhouse describes how to improve phage display ... [not] an animal virus vector such as vaccinia virus to create expression libraries in mammalian host cells" (e.g., see 12/7/04 Response, paragraph bridging pages 31-32).

[4] Applicants argue, "The Examiner also has not pointed to any acceptable objective evidence or sound scientific reasoning that would provide motivation to combine "Rowlands, Zauderer, and Waterhouse" (e.g., see 12/7/04 Response, page 32, paragraph 1).

[5] Applicants argue, "One of ordinary skill in the art would not have had a reasonable expectation of success ... [because] one of ordinary skill in the art would not have reasonably expected the that the phage display technology described in Waterhouse could be extrapolated to methods of generating expression libraries of polynucleotides constructed in an animal virus like vaccinia and introduced into mammalian host cells as in the present invention ..." (e.g., see 12/7/04 Response, page 32, paragraph bridging pages 32-33).

[6] Neither Rowlands nor Zauderer would have provided the skilled artisan with a reasonable expectation of success because Rowlands does not describe using libraries of vaccinia virus vectors (e.g., see 12/7/04 Response, page 33, paragraph 1).

[7] Neither Rowlands nor Zauderer would have provided the skilled artisan with a reasonable expectation of success because ... Zauderer does not describe screening first and second vaccinia virus expression libraries encoding immunoglobulins (e.g., see 12/7/04 Response, page 33, paragraph 1).

This is not found persuasive for the following reasons:

[1] The Examiner respectfully disagrees. For example, the Examiner previously stated, "In addition, Waterhouse et al. teach that "associated" light and heavy chains are a "preferred" embodiment for screening and/or affinity maturation because they can be "simultaneously co-selected" (e.g., see Waterhouse et al., page 2265, paragraph 2), which would encompass the "associated" heavy/light chains described by Rowlands et al" (e.g., see page 22, paragraph 1 of

the 9/7/04 Rejection), which explicitly refers Applicants' to "page 2265, paragraph 2" of Waterhouse et al. In addition, many other citations were provided (e.g., see page 22, paragraph 1 of the 9/7/04 Rejection wherein Zauderer et al., page 22, lines 14-17 were explicitly references; see also page 19, paragraph 1, wherein the Waterhouse et al. reference was again cited to show general motivation for producing antibody libraries in general). Thus, Applicants' assertion that the Examiner has "pointed to nothing specific" within the references is clearly not supported in fact.

[2] In response to applicant's arguments against the Zauderer et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

[3] In response to applicant's arguments against the Waterhouse et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

[4] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, It would have been obvious to one skilled in the art at the time the invention

was made to make a library of vaccinia virus vectors as taught by Zauderer et al. to express fully functional antibodies as taught by Rowlands et al. for the purpose of screening and/or affinity maturation as taught by Waterhouse et al. because Zauderer et al. explicitly state that their libraries can be efficiently produced using the tri-molecular recombination approach with the vaccinia virus vectors (like the vaccinia virus vectors disclosed by Rowlands et al.) and Waterhouse et al. teach that such a library would be useful in screening and affinity maturation. Thus, one of ordinary skill in the art would have been motivated to make the libraries as taught by Zauderer et al. using the heavy/light chain antibodies as disclosed by Rowlands et al. [i.e., ***combine the references***] because Zauderer et al. explicitly state that the their "tri-molecular" approach represents an easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells, which is a preferred embodiment for Rowlands et al. (e.g., see Zauderer et al., page 22, lines 14-17, "Major advantages of these infectious [vaccinia] viral vectors are ... the ease and efficiency with which recombinants can be introduced mammalian cells"). In addition, Waterhouse et al. teach that "associated" light and heavy chains are a "preferred" embodiment for screening and/or affinity maturation because they can be "simultaneously co-selected" (e.g., see Waterhouse et al., page 2265, paragraph 2; see also page 2265, column 1; see also paragraph bridging pages 2265-2266 wherein the usefulness of combinatorial antibody libraries is disclosed), which would encompass the "associated" heavy/light chains described by Rowlands et al. [i.e., ***combine the references***].

[5] In response to applicant's arguments against the Waterhouse et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208

USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, Applicants' response fails to appreciate the combined teachings of "all" the references. Specifically, Applicants' response fails to appreciate the teachings of the Zauderer et al. reference, which does teach the use of an expression library in a mammalian host using an animal virus like vaccinia (e.g., see Zauderer et al., page 52, lines 13-16, "The high yield of viral recombinants in tri-molecular recombination makes it possible, for the first time, to efficiently construct genomic or cDNA libraries in a vaccinia virus derived vector"; see also page 15, paragraph 1; see also page 22, last two paragraphs; see also Example 6 on pages 42-52).

[6] In response to applicant's arguments against the Rowlands et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, Applicants' response fails to appreciate the combined teachings of "all" the references. Specifically, Applicants' response fails to appreciate the teachings of the Zauderer et al. reference, which does teach the use of an expression library in a mammalian host using an animal virus like vaccinia (e.g., see Zauderer et al., page 52, lines 13-16, "The high yield of viral recombinants in tri-molecular recombination makes it possible, for the first time, to efficiently construct genomic or cDNA libraries in a vaccinia virus derived vector"; see also page 15, paragraph 1; see also page 22, last two paragraphs; see also Example 6 on pages 42-52). Furthermore, a person of skill in the art would have had a reasonable expectation of success as outlines in the above rejection (e.g., Zauderer et al. teach several successful examples of library formation using the same vaccinia virus vectors that are disclosed by Rowlands et al. and

Waterhouse et al. teach several successful examples of associated light/heavy chains that can be used for screening and/or antibody maturation, which would encompass the heavy/light chain antibodies disclosed by Rowlands et al.").

[7] In response to applicant's arguments against the Zauderer et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, Applicants' response fails to appreciate the combined teachings of "all" the references. Specifically, Applicants' response fails to appreciate the combined teachings of Zauderer et al. (which teaches a library, for example, at page 52, lines 13-16, "The high yield of viral recombinants in tri-molecular recombination makes it possible, for the first time, to efficiently construct genomic or cDNA ***libraries*** in a ***vaccinia virus*** derived vector"; see also page 15, paragraph 1; see also page 22, last two paragraphs; see also Example 6 on pages 42-52) and Rowlands et al. and Waterhouse et al. that teach the use of an immunoglobulin. For example, Rowlands et al. (see entire document) teach a method for producing antibodies in vaccinia infected cells that reads on the presently claimed invention (e.g., see Rowlands et al., abstract). For example, Rowlands et al. teach **[a-c]** the use of a population of mammalian host cells (e.g., see page 4, paragraph 2; see also paragraph bridging pages 7-8) for introducing and expressing a first/second polynucleotide encoding, through operable association with a transcriptional control region a first/second ***immunoglobulin*** polypeptide comprising both heavy/light chain constant/variable regions and a signal peptide for secretion using a vaccinia virus vector (e.g., see claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a

polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter"; see also page 2, middle paragraph, "An antibody molecule is composed of two light chains and two heavy chains ... Each heavy chain has at one end a variable domain followed by a number of constant domains, and each light chain has a variable domain at one end and a constant domain at the other end"; see especially page 4, second full paragraph, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form").

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Double Patenting

9. Claims 84, 88-97, 99, 103, 107-122 and 127-131 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-84 of U.S. Patent Application Pub. No. 2003/0104402 A1 (referred to herein as '402) (i.e., Application No. 10/052,942) in view of Rowlands et al. (WO 93/01296) (Date of Patent is **January 21, 1993**).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examiner application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1986).

Here, claims 1-84 of U.S. Patent No. '402 recite a method for selecting polynucleotides which encode immunoglobulin molecules which is essentially the same as that disclosed by claims 84, 88-97, 99, 103, 107-122 and 127-131 in the present application (e.g., both methods disclose eukaryotic host cells, a first and second library of polynucleotides encoding immunglobulin light/heavy chain constant/variable regions, permitting expression of said immunoglobulin molecules, contacting the molecules with an antigen, recovering the polynucleotides that encode for immunoglobulins that bind to said antigens, etc). The method of claims '402 differ from the present application in that they claim "intracellular" as opposed to "extracellular" expression.

However, Rowlands et al. teach the use of a population of mammalian host cells (e.g., see page 4, paragraph 2; see also paragraph bridging pages 7-8) for introducing and expressing a first/second polynucleotide encoding, through operable association with a transcriptional control region a first/second immunoglobulin polypeptide comprising both heavy/light chain constant/variable regions and a signal peptide for secretion using a vaccinia virus vector i.e., "extracellular" expression (e.g., see claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter"; see also page 2, middle paragraph, "An antibody molecule is composed of two light chains and two heavy chains ... Each heavy chain has at one end a variable domain followed by a number of constant domains, and each light chain has a variable domain at one end and a constant domain at the other end"; see especially page 4, second full paragraph, "It has now been found that vaccinia virus

vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form"). Rowlands et al. do not explicitly state that a "signal" peptide is being used, but the Examiner contends that this feature is inherent in the method disclosed by Rowlands et al. because the fully functional recombinant antibody would not be "secreted" unless it has such a sequence i.e., Rowlands et al. teach "extracellular" expression. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Thus, it would have been obvious to modify the method of claims 1-84 of U.S. Patent Pub. No. '402 such that "extracellular" expression was performed instead of "intracellular" expression because Rowlands et al. teach that "extracellular" expression may be obtained within Applicants' preferred vaccinia virus vector. One having ordinary skill in the art would have been motivated to make such a modification because Rowlands et al. teach that their "extracellular" expression is particularly well suited for genes of mammalian origin (e.g., see page 4, first full paragraph), which is a preferred embodiment of the '402 patent application (e.g., see claim 26 of '402). In addition,

Rowlands et al. teach that their "extracellular" expression techniques are advantageous "particularly in terms of versatility and speed [because] ... [the] virus will infect a wide range of cells [and] ... [thus] Cell lines suitable for production of a recombinant antibody can thus be derived conveniently and quickly. (e.g., see Rowlands et al., paragraph bridging pages 9-10). Furthermore, Rowland et al. teach that "extracellular" screening can be useful in tumor diagnosis and/or analysis (e.g., see page 9, lines 1-4; see also examples wherein Campath antigen is used). Finally, a person of skill in the art would have reasonably expected to be successful because Rowlands et al. explicitly state that the vaccinia virus vectors used in '402 can be manipulated to secrete antibodies (e.g., see especially page 4, second full paragraph, "It has now been found that vaccinia virus vectors [i.e., the animal virus disclosed in '402] can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is ***secreted into the medium*** and can thus be recovered in functional form").

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response

10. Applicant's arguments directed to the above double patenting rejection were fully considered but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "One of ordinary skill in the art would not have had a reasonable expectation of success in combining Rowlands with the '402 publication ... Rowlands describes the use of vaccinia virus vectors for making an individual recombinant antibody, not an immunoglobulin expression library" (e.g., see 12/7/04 Response, page 34, paragraph 2).

[2] Applicants argue, "... if the Examiner is not inclined to withdraw the rejection, then Applicants respectfully request that it be held in abeyance until such time as otherwise patenatable subject matter has been identified ... At that time, Applicants will consider filing a terminal disclaimer to obviate the double-patenting rejection" (e.g., see 12/7/04 Response, page 34, last paragraph).

This is not found persuasive for the following reasons:

[1] In response to applicant's arguments against the Rowlands et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, Applicants' response fails to appreciate the combined teachings of "all" the references. Specifically, Applicants' response fails to appreciate the teachings of the '402 publication, which does disclose an immunoglobulin expression library (e.g., see claim 1 of '402, "introducing into said population of host cells a ***first library*** of polynucleotides encoding ... a plurality of first intracellular ***immunoglobulin subunit polypeptides*** ... introducing into said population of host cells a ***second library*** of polynucleotides encoding ... a plurality of second intracellular ***immunoglobulin subunit polypeptides***"). Finally, a person of skill in the art would have reasonably expected to be successful because Rowlands et al. explicitly state that the vaccinia

virus vectors used in '402 can be manipulated to secrete antibodies (e.g., see especially page 4, second full paragraph, "It has now been found that vaccinia virus vectors [i.e., the animal virus disclosed in '402] can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is ***secreted into the medium*** and can thus be recovered in functional form") i.e., both references use the same virus (i.e., vaccinia) to express the same molecule (i.e., antibody) and thus would be expected to behave in the same way.

[2] The provisional rejection will not be held in abeyance (e.g., see MPEP § 804 B. Between Copending Applications—Provisional Rejections, "The 'provisional' double patenting rejection ***should continue to be made by the examiner*** in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications."). Here, a double patenting rejection is NOT the only rejection remaining in one of the applications and thus the double patenting rejection is proper.

Accordingly, the double patenting rejection cited above is hereby maintained.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
April 18, 2005